PATENT COOPERATION TREATY

PCT

REC'D 25 AUG 2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-33209A/USN	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/005434	International filing date *(day/month/year)* 19.05.2004	Priority date *(day/month/year)* 20.05.2003
International Patent Classification (IPC) or national classification and IPC C07D413/12, C07D417/12, C07D403/12, C07D207/16, A61K31/427, A61P5/50		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.11.2004	24.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/005434

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-52 as originally filed

   Claims, Numbers

   1-33 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 22-25

because:

☒ the said international application, or the said claims Nos. 22-25 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,8-21,24,27
	No:	Claims	1-5,7,22-23,25-26,28-33
Inventive step (IS)	Yes:	Claims	21
	No:	Claims	1-20,22-33
Industrial applicability (IA)	Yes:	Claims	1-21,26-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

The application is directed to

(i) N-acyl nitrogen heterocycles of formula (I) (claims 1-21),
(ii) therapeutic methods involving compounds (I) (claims 22-25),
(iii) a pharmaceutical compositions comprising compounds (I) (claims 26-28), and
(iv) the medical use of compounds (I) or the corresponding pharmaceutical composition (claims 29-33).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 22-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: EP-A-0 915 088, 12 May 1999.
D2: US-A-5 045 540, 3 September 1991.
D3: WO 00/59874 A, 12 October 2000.
D4: GANTE, J. *ET AL. CHEMIKER-ZTG.* **1985**, *109*, 155-156.
D5: WO 03/043985 A, 30 May 2003.
D6: WILLSON, T M. *ET AL. CURRENT OPINION IN CHEMICAL BIOLOGY* **1997**, *1*, no. 2, 235-241.
D7: RAMI, H. K. *ET AL. EXPERT OPINION ON THERAPEUTIC PATENTS* **2000**, *10*, no. 5, 623-623.
D8: COLLINS, J. L. *ET AL. JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY* **1998**, *41*, 5037-5054.

D5 was published after the priority date. Under the presumption that the priority is valid for the claimed matter the said document is not considered as prior art under Rule 64.1 PCT.

2 Novelty

2.1 **D1** discloses already compounds (I) for the same therapeutic indications as the present compounds (I) (cf. claim 1, formula I-A; e.g. examples 13, 65b, 72b, 74d, 75d; and pages 3-4, paragraph 0004), thereby resulting in a lack of novelty of present claims 1-5, 7, 22-23, 25-26, and 28-33. In order to render the claimed matter novel over **D1**, the whole overlapping range has to be removed from the present set of claims. It is noted that the claimed matter cannot be rendered novel vis-à-vis **D1** by means of disclaimers, because due to the therapeutic indications of the compounds of **D1** the document cannot be considered as an accidental anticipation, which is so remote and unrelated from the claimed invention that the skilled person would never have considered it for the present invention.

D2 relates to angiotensin II antagonists for the treatment of hypertension and heart failure alike the present compounds (I). The compounds of **D2** generally comprise already certain compounds (I) wherein Z and Q are bonds, p is 1, and W is imidazolyl and triazolyl. Furthermore, the document discloses a specific (W)2-butyl-4-chloro-5-hydroxyimidazol-1-yl derivative (example 18) within the overlapping range. Although this compound has been excluded from present claim 1 by means of a disclaimer, the present claims 1, 22-23, 25-26, and 28-33 lack novelty in view of **D2**, because the teaching of the document is not merely limited to compounds (I) wherein W is 2-butyl-4-chloro-5-hydroxyimidazol-1-yl as represented by the specific example. Again it is noted that the document cannot be considered as an accidental anticipation, such that the whole overlapping range has to be removed from present claim 1 in order to render the claimed matter novel vis-à-vis **D2**.

D3 relates to inhibitors of matrix metalloproteinases, TNF, and aggrecanase e.g. for the treatment of arthritis, tumour growth, cardiovascular effects alike the present compounds (I). The compounds of **D3** generally comprise already certain compounds (I) (cf. **D3**, claim 1: A = COOH, $COOR^6$; R^1 and $R^{b'}$ together form a cyclic amine; $R^4 = R^{4a} = H$ or alkyl; and Z^a within R^3 = a C_{3-13}carbocyclic residue or a 5-14 membered heterocyclic system). Furthermore, the document discloses

already specific embodiments within the overlapping range wherein R^3 is 4-[2-methyl-4-quinolinyl)methoxy]phenyl (cf. e.g. examples 33c and 33d; and the corresponding intermediates of examples 34, 36, and 41). Although the 4-[2-methyl-4-quinolinyl)methoxy]phenyl examples of **D3** are excluded from present claim 1 by means of a disclaimer, the present claim 1 lacks novelty in view of the document, because its teaching is not limited to the (R^3)4-[2-methyl-4-quinolinyl)methoxy]phenyl examples (without being limitative cf. e.g. R^3 of examples 18, 20-22, 24, etc.). Consequently, the whole overlapping range has to be removed from present claim 1 in order to render the claimed matter novel over **D3**. The present claims 22-23, 25-26, and 28-33 are not considered to lack novelty in view of **D3**, because the active compounds of the document appear to represent exclusively hydroxamic acids (A = CONHOH) rather than carboxylic acids or esters thereof.

D4 relates to a carboxamide synthesis and discloses a compound (I) wherein L is (II), R^1 is t-butyl, X^2 is NH, Z is NHCO, p is 1, Q is CONH, and W is phenyl (**D4**, compound 4f). Present claim 1 lacks thus novelty in view of **D4**.

D6 to **D8** disclose peroxisome proliferator-activated receptor (PPAR) ligands. In this context, the documents disclose compounds that show certain structural features of the present compounds (I) (**D6**, indomethacin comprising a indolyl-1-yl moiety similarly to the present structure (III); **D6** and **D7**, LY171883, comprising a R,R',X^1-phenyl moiety similarly to the present moiety of (I); **D7**, compound 9, and **D8**, compound 2, comprising a R,R',X^1-phenyl moiety similarly to the present moiety of (I)). These documents are, however, not relevant to the question of novelty of the present application, because the present compounds (I) are not disclosed therein.

2.2 **D5** relates to further PPAR ligands from which the present compounds (I) differ insofar as they represent N-acyl (cf. the moiety -C(O)X^2-) rather than N-sulfonyl nitrogen heterocycles. The document will thus not become relevant to the question of novelty of the present claimed matter.

3 Inventive Step

Insofar as the application relates to novel subject matter the following observations apply to the requirements of inventive step.

3.1 The application describes the synthesis of certain compounds (I) and reports that one such compound (i.e. example 9, cf. the application, page 41) binds to PPARα and PPARγ. Accordingly, the claimed compounds are believed to be useful in the treatment of diseases such as heart failure, cardiovascular diseases, arthritis, cancer, diabetes and other pathological conditions.

3.2 The documents **D6** to **D8** describe already compounds of the desired activity. The present compounds (I) differ from those of said prior art (e.g. **D6**, LY171883; **D7**, GI262570 **9**, and LY171883 **19**; **D8**, compound **2** and those of tables 1-5) through their L-C(O)-X^2- moiety. Starting from one of these documents as most relevant state of art, the problem underlying the application may be seen in the provision of further PPAR ligands. Although, indomethacin as disclosed in **D7** comprises already an indolyl moiety similarly to the present (L)moiety of structure (III), none of the cited documents hints or suggests that the present L-C(O)-X^2-substituted compounds (I) might exhibit the desired activity. Consequently, based on the unexpected retention of the desired activity as shown for example 9, an inventive step may be acknowledged for novel compounds (I) according to claim 21 as well as plausible generalisations thereof.

However, the terms such as "optionally substituted", "alkyl", "aryl", "heteroaryl", "aralkyl", "cycloalkyl", "5- to 7-membered ring", etc. used in claims 1-20 are open-ended and thus likely to comprise structures which will not solve any relevant technical problem. Consequently, no inventive step would be acknowledged for compounds (I) comprising such open-ended groups and subject matter referring to such compounds (I). Hence, the claims 1-20 and 22-33 lack inventive step.

4 Industrial Applicability

For the assessment of the present claims 22-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such

a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 03/043985 A	30.05.2003	20.11.2002	21.11.2001

Re Item VII

Certain defects in the international application

The relevant background art disclosed in **D1** to **D4** and **D6** to **D8** is not mentioned in the description, nor are these documents identified therein (Rule 5.1(a)(ii) PCT), although in view of the disclaimers in present claim 1 the applicant appears to be familiar with at least some of the relevant prior art. The applicant is advised that the ISA does not appreciate this practice.

Re Item VIII

Certain observations on the international application

The present set of claims does not comply with the requirements of Article 6 PCT for the following reasons.

1 The term "lower alkyl" used in the claims lacks clarity with regard to the maximum number of carbon atom which distinguishes "lower alkyl" from non-lower alkyl. Furthermore, the definitions of cycloalkyl, aryl, and heterocyclyl as comprising the corresponding substituted groups (cf. the description) are not generally accepted in the art (Rule 10.1(e) PCT). These definitions imply that the subject-matter for which protection is sought might be different from what is defined in the claims, thereby resulting in a lack of clarity of the claims. These objections may be overcome by inserting into the claims the respective definitions provided in the description. The applicant is reminded that the exact definitions of the objected terms in the description alone is not sufficient for the claims to be clear.

2 Claims 23, 30, and 31 are not acceptable under Article 6 PCT, because the

therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. Independent from this reasoning, the vague phrase "associated with PPAR activity" as used in claims 30 and 31 renders these claims incomprehensible.

3 Finally, the terms "derivative", "mimetic", "secretagogue", and "analog" used in claims 24 and 27 render the claims unclear, because it is not evident which structural features of the parent compounds (e.g. of insulin or GLP-1) must necessarily be present in said derivatives, mimetics, secretagogues, and analogs and which structural features may be varied. Without being limitative it remains e.g. unclear whether CO_2 and H_2O (e.g. derived from insulin or GLP-1 during combustion analysis) would be considered e.g. as "insulin derivatives" or "GLP-1 analogs".